BIOENERGETICALLY ACTIVE ESTERS FOR HEALTH AND DISEASE

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Application 62/739,275, filed Sep. 30, 2018, the entire contents of which are incorporated herein by reference.

STATEMENT OF FEDERALLY FUNDED RESEARCH

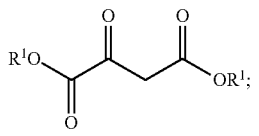
[0002] This invention was made with government support under NS077852 and AG060817 awarded by the National Institutes of Health. The government has certain rights in the invention.

FIELD

[0003] The present technology is directed to compounds, compositions, and methods useful in modulating bioenergetic metabolism. For example, this technology is particularly suited to promote bioenergetic processes including cellular respiration and glycolytic flux. Accordingly, the compounds and compositions may be used to treat neurodegenerative diseases such as Alzheimer's disease (AD).

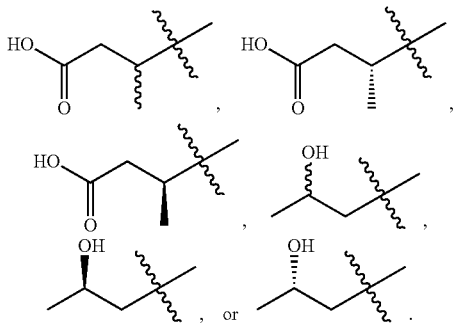
SUMMARY

[0004] In an aspect, a compound of Formula I is provided:



(I)

or a pharmaceutically acceptable salt and/or solvate thereof, wherein both R^1 are selected from:



[0005] In an aspect, the present technology also provides compositions that include any embodiment of a compound of the present technology as disclosed herein and a pharmaceutically acceptable carrier.

[0006] In a related aspect, the present technology provides pharmaceutical compositions that include an effective amount of any embodiment of the compounds disclosed herein (or a pharmaceutically acceptable salt and/or solvate of any thereof) and a pharmaceutically acceptable carrier, wherein the effective amount is effective for increasing cellular respiration in a subject, increasing glycolytic flux in a subject, and/or treating a subject suffering from a neurodegenerative disease (e.g., Alzheimer's disease), multiple sclerosis, and/or epilepsy.

[0007] Further aspects are directed to methods of use of a compound of the present technology, including methods of treatment by administration of a compound of the present technology.

BRIEF DESCRIPTION OF THE DRAWINGS

[0008] FIGS. **1**A-**1**D provide that a 2-oxosuccinic acid (oxaloacetic acid or OAA) bioenergetic treatment increased cellular respiration by ~50%, similar to glucose restriction, and also increased glycolysis flux capacity by about 50%, according to the working examples. In particular, FIG. **1**A provides the NAD$^+$/NADH ratio upon addition of exogenous OAA; FIGS. **1**B-**1**C illustrate the increased glycolysis rate (FIG. **1**B) and increased respiration rate (FIG. **1**C) provided by administering OAA in SH-SY5Y human neuroblastoma cells; and FIG. **1**D provides an overall illustrative schematic of bioenergetic flux. **p<0.01. For the sake of clarity, for FIG. **1**B the data is presented (going from left to right) as CON, 2 mM OAA, 2 mM MA, and 2 mM PYRUVATE; for FIG. **1**C, the data is presented (going from left to right) as CON. OAA, MALATE, GLUCOSE DEPRIVATION, and PYRUVATE.

[0009] FIG. **2** illustrates that 3,3'-((2-oxosuccinyl)bis(oxy))dibutyric acid) (also referred to herein as "OAA $(BHB)_2$") of the present technology increases SH-SY5Y neuroblastoma cell respiration ~30% at a 1-mM dose, where CON=saline, oligomycin blocks ATP-stimulated respiration, FCCP uncouples respiration (illustrates maximum possible rate), and rotenone/antimycin A are respiratory inhibitors in presence of FCCP. Data are averages of three experiments.

[0010] FIGS. **3**A-**3**B illustrate the effect of bis(2-hydroxypropyl) 2-oxosuccinate (also referred to herein as "OAA $(PG)_2$") of the present technology on bioenergetic fluxes, according to the working examples. FIG. **3**A provides the oxygen consumption rate (OCR; indicative of cellular respiration) over time of SH-SY5Y neuroblastoma cells after the addition of differing concentrations OAA$(PG)_2$ in comparison to a control as well as to background values, and FIG. **3**B charts the effect that OAA$(PG)_2$ concentrations have on glycolysis in SH-SY5Y neuroblastoma cells, evidencing that OAA$(PG)_2$ concentrations that enhance respiration have an insignificant effect on glycolysis. ECAR=extracellular acidification rate. For the sake of clarity, for FIG. **3**B the data are presented (going from left to right) as Control, 1 mM OAA$(PG)_2$, 2 mM OAA$(PG)_2$, and 5 mM OAA$(PG)_2$.

[0011] FIG. **4** provides the OCR over time of SH-SY5Y neuroblastoma cells after the addition of differing concentrations OAA$(PG)_2$ in comparison to a control as well as background values, according to the working examples. Data are average of three experiments.

[0012] FIGS. **5**A-**5**B show OAA$(D\text{-}BHB)_2$ (referred to as "OAA-D-BHB" in these figures) increases plasma BHB levels. FIG. **5**A shows ketone levels before and 45 min after administration of OAA$(D\text{-}BHB)_2$ on the first and second days of the experiment according to the present examples. FIG. **5**B shows ketone level fold-change as a function of that day's baseline.